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(54) Title: SWALLOWABLE PHARMACEUTICAL COMPOSITIONS CONTAINING COLLOIDAL BISMUTH SUBCITRATE

(57) Abstract

Oral pharmaceutical compositions in unit dosage form suitable for swallowing (especially capsules) comprising a safe and effective amount of solid Colloidal Bismuth Subcitrate (CBS), and optionally one or more pharmaceutically-acceptable carrier materials, wherein the packing density of the dosage unit is less than about 1 g/ml.

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SWALLOWABLE PHARMACEUTICAL COMPOSITIONS CONTAINING COLLOIDAL BISMUTH SUBCITRATE

BACKGROUND OF THE INVENTION

The present invention relates to low density oral pharmaceutical compositions in unit dosage form suitable for swallowing comprising solid Colloidal Bismuth Subcitrate.

Solid Colloidal Bismuth Subcitrate ("CBS"; Trademark De-Nol® of Gist-brocades N.V.) is the product of European Patent 0,075,992, corresponding to U.S. Patent 4,801,608. It is also the active ingredient of British Patent 1,478,742. According to these specifications, CBS can be formulated into pharmaceutical compositions in solid dosage form for oral administration, such as tablets and capsules. Up to now only the tablet form (both chewable and swallowable tablets) has been realized and it is marketed in many countries.

The currently used swallowable tablet form of CBS has already been given to hundreds of thousands of patients and its clinical efficacy and safety are firmly established. However, recently there have been reports of a transient sharp peak of bismuth blood level in humans after the ingestion of this CBS-containing swallowable tablet, t_{max} around 30 minutes (see C.U. Nwokolo et al, Aliment. Pharmacol. Therap., 3, 1989, 29-39). Since the therapeutic action of CBS is believed to be localized in the gastrointestinal tract, even a transient peak of bismuth blood level does not appear to serve any useful purpose and it is therefore desirable to minimize bismuth blood levels if possible.

It has been discovered that this currently used tablet form (having a density greater than 1 g/ml), in vitro in liquid acidic medium, has a tendency to sink to the bottom of the liquid and dissolve by first forming liquid CBS solution rather than the desired insoluble bismuth precipitate. By contrast, unit dosage forms (as according to the present invention) which are less dense than the current tablet form and also less dense than the acidic medium (approximately 1 g/ml) do not form this initial CBS liquid

but rather quickly forms the desired insoluble bismuth precipitate. Interestingly, when these low density unit dosage forms are weighted to the bottom of the test liquid, again the CBS initially liquifies.

A low packing density of oral dosage units as specified above is contrary to the current tendency in the art of pharmaceutical production, which is to concentrate the oral dosage units, e.g. by compressing the contents of oral capsules to a high density (see Hard Capsules, Development and Technology, Ed. K. Ridgway 1987, chapter 9, G.C. Cole, pp. 92-103).

That the low density unit dosage form of the present invention in fact substantially reduces bismuth blood levels as predicted by these different in vitro characteristics has been confirmed by in vivo testing. The oral dosage units of the present invention, when compared to swallowable tablets comprising the same formula and dosage of CBS but with a higher density, were found to give not only a lower maximal blood plasma bismuth level (C_{max}), but also a lower blood plasma bismuth rise (AUC) and a lower bismuth excretion in the urine. Therefore, systemic bismuth absorption after ingestion of the dosage units of the present invention has proved to be lower than after ingestion of the prior swallowable tablets. This is contrary to what one might expect - that less dense and thereby more dispersible material would lead to more rapid dissolution and consequently to greater absorption than compressing to higher density the same material.

Thus, the oral dosage units of the present invention surprisingly give peak bismuth plasma levels and a total bismuth absorption which are lower than that of the denser dosage units.

An object of the present invention therefore is to provide an oral dosage unit suitable for swallowing comprising CBS in a therapeutically effective amount which substantially reduces bismuth absorption and thereby the above described peak in the bismuth blood levels.

This and other objects of the present invention will become readily apparent from the detailed description which follows.

All percentages and ratios used herein are by weight, and all measurements made at 25°C, unless otherwise specified.

SUMMARY OF THE INVENTION

The present invention relates to oral pharmaceutical compositions in unit dosage form suitable for swallowing comprising a safe and effective amount of solid colloidal bismuth subcitrate and, optionally, pharmaceutically-acceptable carrier materials, wherein the packing density of the pharmaceutical composition is less than about 1 g/ml.

The present invention also relates to a method for manufacturing unit dosage forms suitable for swallowing comprising solid colloidal bismuth subcitrate. Said method comprises the step of forming a unit dosage of a dry composition comprising solid colloidal bismuth subcitrate having a packing density of less than about 1 g/ml. Preferred is the method wherein a dry particulate composition comprising solid colloidal bismuth subcitrate is filled into a capsule to a packing density of less than about 1 g/ml.

The present invention further relates to methods for treating or preventing gastrointestinal disorders in humans or lower animals. These methods comprise orally administering by swallowing to a human or lower animal in need of such treatment or prevention a safe and effective amount of an oral pharmaceutical composition according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

(1) Oral Pharmaceutical Compositions:

The oral pharmaceutical compositions of the present invention comprise colloidal bismuth subcitrate ("CBS") in unit dosage forms suitable for swallowing (eg., tablets and, especially, capsules) wherein the packing density of the composition is less than about 1 g/ml. Preferably, these compositions comprise the CBS and a pharmaceutically-acceptable carrier material(s).

The term "packing density," as used herein, means the weight of the drug mixture (active CBS ingredient plus carrier materials) in grams divided by the volume occupied by the dose form expressed in milliliters, and, in case of a filled capsule form, excludes the volume and weight of the capsule container. Thus, the packing density can be varied by varying the types and amounts of

excipients added to the CBS and especially by varying the pressure used in compressing the units. Oral pharmaceutical compositions herein have packing density of less than about 1 g/ml, preferably within the range of from about 0.05 g/ml to less than about 1 g/ml, more preferably from about 0.25 g/ml to about 0.9 g/ml, and most preferably from about 0.5 g/ml to about 0.75 g/ml.

The particular agents for use herein, as well as the levels and amounts preferred therefor, are described in greater detail hereinafter.

(a) Colloidal Bismuth Subcitrate:

Colloidal bismuth Subcitrate ("CBS") is described in The Merck Index, 11th Edition (1989), item 1296 (incorporated herein by reference in its entirety), to have the approximate molecular formula of $K_3(NH_4)_2[Bi_6O_3(OH)_5(C_6H_5O_7)_4]$. The preparation and use of CBS is described in detail in U.S. Patent 4,801,608, to Bos et al, issued January 31, 1989; and Great Britain patent specification 1,478,742, published July 6, 1977 by Gist-brocades, N.V., the disclosures of both these patents being incorporated herein by reference in their entirety. The CBS used in the compositions of the present invention (preferably including any optional carrier materials) is preferably in the form of granules or powders, having a preferred particle size of less than about 1.5mm.

The oral pharmaceutical compositions herein comprise a safe and effective amount of CBS, typically in the amount of from about 30 mg to about 600 mg per dosage unit, and preferably from about 37.5 mg to about 300 mg per dosage unit. As a percentage of the oral pharmaceutical compositions, CBS typically comprises from about 1% to about 100%, and preferably from about 25% to about 99%, by weight of the composition.

(b) Pharmaceutically-Acceptable Carrier Materials:

The oral pharmaceutical compositions herein may also optionally comprise one or more pharmaceutically-acceptable carrier materials. The term "pharmaceutically-acceptable carrier materials," as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are

suitable for oral administration to a human or lower animal. The term "compatible," as used herein, means that the components of the oral pharmaceutical composition are capable of being commingled with the CBS, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the pharmaceutical composition under ordinary use situations by swallowing the composition. Pharmaceutically-acceptable carrier materials must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for oral administration to the human or lower animal being treated.

To the CBS may be added any of the pharmaceutically-acceptable carrier materials known in the art, which are compatible with CBS, such as:

- diluents, like lactose, starch, microcrystalline cellulose, sorbitol, mannitol, dibasic calcium phosphate dihydrate, calcium sulfate dihydrate, sucrose-based diluents and mixtures thereof;
- binders, like acacia, cellulose derivatives, gelatin, glucose, polyvinylpyrrollidone, starch, sucrose, sorbitol, tragacanth, sodium alginate and mixtures thereof;
- disintegrants, like microcrystalline cellulose and cellulose derivatives, starch and its derivatives, alginic acid and its derivatives, ion-exchange resins, cross-linked sodium carboxymethyl cellulose, sodium starch glycolate, cross-linked polyvinylpyrrollidone and formaldehyde-caseine;
- lubricants, antiadherents and glidants, like magnesium-, calcium- and sodium stearates, stearic acid, hydrogenated castor oil, talc, water, polyethylene glycol, sodium laryl sulfate, magnesium laryl sulfate and silica.

Furthermore, the pharmaceutically-acceptable carrier materials may also comprise one or more auxiliary medicaments, preferably those which are intended to act in combination with it, such as non-steroidal anti-inflammatory compounds, H_2-antagonists, cytoprotectants (e.g., sucralfate), and synthetic prostaglandins. In particular the dosage units may contain antimicrobially

effective medicaments such as antibiotics and chemotherapeutic compounds, more in particular medicaments effective against Campylobacter pylori (recently renamed Helicobacter pylori), such as the antimicrobially effective imidazoles, in particular metronidazole and tinidazole, penicillins, cephalosporins, tetracyclines, chinolones and macrolides. The dosage of the optionally present auxiliary medicaments will depend on the effectivity of the particular medicament used. Optional auxiliary medicaments useful herein are described in detail in: European Patent Application Publication No. 206,625, published December 30, 1986, by Marshall; and International Publication No. WO 86/05981, published October 23, 1986, by Borody, the disclosures of both these publications being incorporated herein by reference in their entirety.

The most preferred oral dosage units according to the invention are capsules, although tablets having a low density as defined above are also possible. The material of swallowable capsules according to the invention may be any of those known in the art, such as gelatine, modified starches, such as hydroxyalkyl starch, and cellulose derivatives, such as cellulose ethers, e.g. methyl cellulose. Preferably, the capsule material and size of the capsule are chosen such that the capsule unit dosage form filled with the drug mixture has a density of less than about 1 g/ml. Gelatine capsules can be soft and hard. The dosage units according to the invention may be further coated in order to provide for controlled release.

The oral pharmaceutical compositions herein preferably comprise from about 3 mg to about 1000 mg, more preferably from about 20 mg to about 150 mg, of pharmaceutically-acceptable carrier material per 100 mg of CBS. As a percentage of the oral pharmaceutical compositions, pharmaceutically-acceptable carrier materials comprise from about 0% to about 99%, and preferably from about 1% to about 75%, by weight of the composition.

The method of manufacturing unit dosage forms suitable for swallowing comprising CBS, according to the present invention, preferably comprises the step of forming a unit dosage of a dry

composition comprising CBS having a packing density of less than about 1 g/ml. Preferred is the method wherein a dry particulate composition (e.g., granulate; powder) comprising CBS is filled into a capsule to a packing density of less than about 1 g/ml.

(2) Methods for Treating or Preventing Gastrointestinal Disorders:

Another aspect of the present invention is methods for treating or preventing gastrointestinal disorders in humans or lower animals. Such methods comprise orally administering by swallowing, to a human or lower animal in need of such treatment or prevention, a safe and effective amount of an oral pharmaceutical composition according to the present invention.

The term "gastrointestinal disorder," as used herein, encompasses any disease or other disorder of the gastrointestinal tract, preferably the upper gastrointestinal tract, of a human or lower animal treatable or preventable by the CBS useful herein. The term "upper gastrointestinal tract," as used herein, is defined to include the esophagus, the stomach, the duodenum, and the jejunum. Such upper gastrointestinal tract disorders include, for example: disorders not manifested by presence of ulcerations in the gastric mucosa (herein "non-ulcerative gastrointestinal disorders"), including chronic or atrophic gastritis, non-ulcer dyspepsia, esophageal reflux disease and gastric motility disorders; and "peptic ulcer disease," i.e., gastric, duodenal and jejunal ulcers. Included herein are diseases or disorders caused or mediated by Helicobacter pylori.

The phrase "safe and effective amount," as used herein, means an amount of CBS high enough to significantly positively modify the condition to be treated but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of the oral pharmaceutical composition of the present invention will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of treatment, the nature of concurrent therapy, the particular pharmaceutically-acceptable carrier materials utilized, and like factors within the knowledge and

expertise of the attending physician. The methods of the present invention typically involve administering from about 100 mg to about 4800 mg of CBS per day, and preferably from about 200 mg to about 1200 mg per day.

The following examples further describe and demonstrate the present invention. The examples are given solely for the purpose of illustration, and are not to be construed as limitations of the present invention since many variations thereof are possible without departing from its spirit and scope.

EXAMPLE 1

CBS is prepared according to European Patent 0,075,992 and U.S. Patent 4,801,608 (both incorporated herein by reference in their entirety), and is used to prepare tablets and capsules as follows.

Uncoated swallowable tablets containing CBS are produced as follows: 100 kg of CBS is granulated with 23.8 kg of corn starch using 5.85 kg of povidone K30 dissolved in 51.0 kg of ethanol. The granulate, having a particle size of less than 1 mm, is blended with 7.8 kg of polacrilin potassium, 1.98 kg of polyethylene glycol 6000 and 0.66 kg of magnesium stearate, and is compressed into tablets.

Coated swallowable tablets containing CBS are produced by filmcoating the above described compressed tablets with about 12 mg hydroxypropyl methylcellulose and about 2 mg polyethylene glycol per tablet. These tablets are representative of commercially used De-Nol® swallowable tablets.

Reduced density swallowable capsules according to the present invention (having packing densities of 0.6 g of CBS composition/ml and 0.86 g of CBS composition/ml) are produced using the granulate for uncoated swallowable tablets as described above, filled into hard gelatin capsules No. 0, using a rotary capsule filling machine. The packing density of the capsule content is adjusted by settings of the piston within the dosator.

The densities of the uncoated and coated tablets and of the contents of the two different capsules are calculated with respect to the amount of CBS-containing composition per units of volume.

The results are presented in the following Table 1:

Table 1

	Packing volume	Packing density (CBS-containing composition/volume)
Tablet, uncoated	0.25 ml	1.7 g/ml
Tablet, coated	0.25 ml	1.7 g/ml
Reduced Density Capsule #1	0.70 ml	0.6 g/ml
Reduced Density Capsule #2	0.50 ml	0.86 g/ml

EXAMPLE 2

Bismuth absorption in dogs

Healthy fasted dogs (Beagles) are given a single dose of coated tablets or the reduced-density capsules #1 of Example 1. The dogs are each dosed with 2 tablets or 2 capsules, giving a total dose of 600 mg CBS per dog. After ingestion, blood samples are taken at 9 intervals up to 8 hours. The bismuth content is measured in the blood by atomic absorption.

In dogs the reduced density capsules according to the present invention give a lower systemic bismuth absorption (for both the "blood Cmax", which is the maximum bismuth blood level measured at a time after ingestion, and the "blood AUC", which is the Area Under bismuth concentration-time Curve, over an 8 hour period after dosing) than does the prior art tablet dosage form having the same composition but compressed to a higher density.

EXAMPLE 3

Bismuth absorption in humans

Healthy fasted human volunteers are dosed with the uncoated and coated tablets and the two different capsules of Example 1. The volunteers are each dosed with 2 tablets or 2 capsules, giving a total dose of 600 mg CBS per volunteer. After ingestion blood samples are taken at several intervals up to 3 hours, and the urine is collected for 3 hours. The bismuth content is measured in the blood plasma and in the urine by atomic absorption.

In humans the reduced density capsules of the present invention give a much lower systemic bismuth absorption (for both blood Cmax and blood AUC, as well as for bismuth in urine) than

does the prior art dosage form. Furthermore, there appears to be a reverse relationship between the density of the dosage form and the amount of systemic bismuth absorption therefrom, with compositions of packing density less than about 1 g/ml having substantially less bismuth absorbed than the prior art tablet having packing density above 1 g/ml.

Oral administration of the reduced density capsules of the present invention is very effective for treating patients suffering from ulcers and/or Helicobacter pylori infection.

WHAT IS CLAIMED IS:

CLAIMS

1. An oral pharmaceutical composition in unit dosage form suitable for swallowing comprising a safe and effective amount of solid colloidal bismuth subcitrate and, optionally, pharmaceutically-acceptable carrier materials, wherein the packing density of the pharmaceutical composition is less than 1 g/ml.

2. The oral pharmaceutical composition according to Claim 1 wherein the packing density is within the range of from 0.05 g/ml to less than 1 g/ml.

3. An oral pharmaceutical composition in unit dosage form suitable for swallowing according to either of Claims 1 or 2 comprising:
   (a) from 1% to 100% solid colloidal bismuth subcitrate; and
   (b) from 0% to 99% pharmaceutically-acceptable carrier materials;
   and wherein the packing density of the pharmaceutical composition is less than 1 g/ml.

4. The oral pharmaceutical composition according to any of Claims 1-3 wherein each dosage unit comprises from 30 to 600 mg of solid colloidal bismuth subcitrate.

5. The oral pharmaceutical composition according to any of Claims 1-4 further comprising at least one auxiliary medicament.

6. The oral pharmaceutical composition according to any of Claims 1-5 comprising at least one antimicrobial medicament safe and effective against Helicobacter pylori.

7. The oral pharmaceutical composition according to any of Claims 1-6 comprising at least one antimicrobial medicament safe and effective against Helicobacter pylori selected from the group consisting of metronidazole, tinidazole, penicillin, cephalosporin, tetracycline, chinolones, macrolides, or mixture thereof.

8. The oral pharmaceutical composition according to any of Claims 1-7 in unit dosage form of a capsule.

9. An oral pharmaceutical composition in unit dosage form of a capsule suitable for swallowing according to any of Claims 1-8 comprising:
   (a) from 25% to 99% solid colloidal bismuth subcitrate; and
   (b) from 1% to 75% pharmaceutically-acceptable carrier materials;
   and wherein the pharmaceutical composition is filled into a capsule to a packing density within the range of from 0.5 g/ml to 0.75 g/ml.

10. A method for manufacturing unit dosage forms suitable for swallowing according to any of Claims 1-9, said method comprising the step of forming a unit dosage of a dry composition comprising solid colloidal bismuth subcitrate having a packing density of less than 1 g/ml.

11. The use of solid colloidal bismuth subcitrate for the manufacture of a medicament according to any of Claims 1-9 for the treatment or prevention of gastrointestinal disorders in humans or lower animals, said treatment or prevention comprising orally administering to said human or lower animal a safe and effective amount of a medicament according to any of Claims 1-9.

12. A method for treating or preventing gastrointestinal disorders in humans or lower animals, said method comprising orally administering by swallowing to a human or lower animal in need of such treatment or prevention a safe and effective amount of an oral pharmaceutical composition according to Claim 1.

13. A method for treating or preventing gastrointestinal disorders in humans or lower animals, said method comprising orally administering by swallowing to a human or lower animal in need of such treatment or prevention a safe and effective amount of an oral pharmaceutical composition according to Claim 5.

14. A method for treating or preventing gastrointestinal disorders in humans or lower animals, said method comprising orally administering by swallowing to a human or lower animal in need of such treatment or prevention a safe and effective amount of an oral pharmaceutical composition according to Claim 6.

15. A method for treating or preventing gastrointestinal disorders in humans or lower animals, said method comprising orally administering by swallowing to a human or lower animal in need of such treatment or prevention a safe and effective amount of an oral pharmaceutical composition according to Claim 7.

16. A method for treating or preventing gastrointestinal disorders in humans or lower animals, said method comprising orally administering by swallowing to a human or lower animal in need of such treatment or prevention a safe and effective amount of an oral pharmaceutical composition according to Claim 9.

17. A method for manufacturing unit dosage forms suitable for swallowing, said method comprising the step of forming a unit dosage of a dry composition comprising solid colloidal bismuth subcitrate having a packing density of less than about 1 g/ml.

18. The method according to Claim 17 wherein a dry particulate composition comprising solid colloidal bismuth subcitrate is filled into a capsule to a packing density of less than about 1 g/ml.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/00193

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/29 A 61 K 33/24 A 61 K 9/48

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0206625 (B.J. MARSHALL) 30 December 1986, see the claims; page 14, example II	1-18
P,X	EP,A,0437294 (GIST-BROCADES) 17 July 1991, see the whole document	1-18

* Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
06-04-1992	27 APR 1992
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	TAZELAAR

Form PCT/ISA/210 (second sheet) (January 1985)

International Application No. PCT/ US92 /00193

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 12-16 are directed to a method of treatment of the human or animal body by therapy, the search has been carried out and based on the alleged effects of the composition.

2. ☐ Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9200193 SA 56521

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 22/04/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0206625	30-12-86	AU-B-	588601	21-09-89
		AU-A-	5859586	18-12-86
		BE-A-	904921	15-12-86
		CA-A-	1277232	04-12-90
		DE-A-	3619702	12-02-87
		EP-A-	0462631	27-12-91
		JP-A-	62048623	03-03-87
EP-A- 0437294	17-07-91	AU-A-	6869391	11-07-91